Thus, Applicant's invention requires the combination of limitations (a), (b) and (c).

(2) Purpose of the present invention

As described in Applicant's specification, the purpose of the present invention is to provide a stable and clear aqueous solution preparation containing an aminoglycoside antibiotic or its pharmacologically acceptable salt and bromfenac or its pharmacologically acceptable salt. (Please see page 4, lines 9 -12 of the specification.)

(3) Effect of the present invention

By using limitation (c) in combination with limitations (a) and (b), a stable and clear aqueous solution preparation in which no precipitation occurs can be obtained.

Discussion of Reference D1: Fu et al. (US 5,414,011)

D1 discloses an opthalmologically acceptable formulation which comprises ketrolac, tobramycin, a vehicle and a nonionic surfactant (abstract).

In D1, ketrolac and tobramycin are used in Examples 3 and 4 (columns 9 and 10). Further, it is also described in Examples 3 and 4 that "The above ingredients are mixed, adding purified water until they are dissolved, ..." (column 10, lines 6-7 and 30-31). From these descriptions, it is clear that ketrolac, tobramycin, quaternary ammonium preservative and a particular nonionic surfactant are dissolved at pH 7.4. It is further described in column 12, lines 19-25 of D1 that the solution preparations prepared in Examples 3 and 4 were stable for one month and for five months.

On the other hand, it is described in Applicant's specification that, "The inventors of the present invention have intensively studied [on] the above problems, resulting in finding that an aqueous solution preparation containing an aminoglycoside antibiotic and bromfenac does not cause precipitation by adjusting the pH to 7.0 or higher, which was an unexpected finding. However, it was found that precipitation occurred gradually when such aqueous solution was preserved." (Please see page 4, lines 15-21 of Applicant's specification). In fact, it is shown in Example 2 in the specification that there was turbidity occurrance in "Control (no additive)", which was prepared by adding only bromfenac and tobramycin to a borate buffer solution (page

22, Table 5 of the specification).

Thus, Applicant further studied to determine a method where no precipitation occurred, even after preservation. Applicant discovered the specific combination of (a), (b) and (c), as recited in the claims.

The Examiner acknowledges that D1 fails to teach or suggest component (c) of Applicant's claims. Furthermore, those skilled in the art would not have been motivated by D1 to add monoethanolamine or nicotinamide to the aqueous solution in order to obtain clear and stable solution, because a clear and stable solution was obtained in D1.

Discussion of Reference D4: Miyagi et al. (US 6,281,224)

The Examiner relies on D4 to teach Applicant's component (c), i.e., monoethanolamine or nicotinamide.

D4 discloses an ophthalmic solution containing pranoprofen and an organic amine, such as tromethamine.

However, it is important to note that D4 discloses many organic amines, such as tromethamine (column 2, lines 3 to 13). Thus, D4 fails to recognize the specific combination of Applicants' claims, wherein (c) is monoethanolamine or nicotinamide.

On the other hand, in the aqueous solution preparation of the present invention, a clear and stable solution is not obtained by adding N-methylglucamine, which is also an organic amine, but rather is obtained by adding monoethanolamine or nicotinamide. (Please see page 22, Table 5 of Applicant's specification.) Thus, based on the teachings of Miyagi, it would not have been expected that, among organic amines, only monoethanolamine or nicotinamide is effective to inhibit turbidity occurrence in the aqueous solution preparation containing bromfenac and tobramycin, and make the preparation clear.

Accordingly, Applicant's composition has unexpected results, which would not have been obvious to those skilled in the art.

Discussion of References D2: Ogawa et al. (US 4,910,225) and D3: Cagle et al. (US 6,440,964)

Neither D2 nor D3 disclose or suggest limitation (c) of Applicant's claims.

Accordingly, even if references D1-D4 were combined, Applicant's specific combination would not have been obvious. Furthermore, it would not have been obvious to those skilled in the art that a solution which comprises bromfenac, aminoglycoside antibiotic and monoethanolamine or nicotinamide becomes clear and stable.

For the reasons set forth above, it is evident that the subject matter of Applicant's claims is patentable over the cited combination of references. Thus, it is respectfully requested that the above-rejection be withdrawn.

Conclusion

Therefore, in view of the above remarks, it is submitted that the ground of rejection set forth by the Examiner has been overcome, and that the application is in condition for allowance. Such allowance is solicited.

If, after reviewing this response, the Examiner feels there are any issues remaining which must be resolved before the application can be passed to issue, the Examiner is respectfully requested to contact the undersigned by telephone in order to resolve such issues.

Respectfully submitted,

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